REMARKS

Claims 1-15 are pending in this application, and entry of new claim 15 is respectfully requested. New claim 16 specifies that in subparagraph (a), the poly(ethylene glycol)-phospholipid and polyene antibiotic are present in the solution at a molar ratio of from 0.75:1 to 10:1; support is found in as-filed claim 8. Claim 1 has also been amended to specify that the antibiotic is deaggregated. Claim 1 has been amended to provide consistency between the preamble and the whereby clause, thus better claiming the invention. The importance of deaggregation and toxicity are discussed in the application at page 12, first paragraph, for example. Claim 12 has been amended to clarify that mPEG-DSPE is the abbreviation for poly(ethylene glycol)-1,2-di-stearoyl-phosphatidyl ethanolamine. None of the amendments made herein constitutes the addition of new matter.

The Rejections under 35 U.S.C. 103

Claims 1-15 were rejected under 35 U.S.C. 103 as allegedly unpatentable over Onyuksel (US Patent 6,217,886). Applicant respectfully traverses this rejection.

Onyuksel is said to disclose a method of preparing micelles containing the polyene compounds Amphotericin B (Am B) and Nystatin. The method is said to involve dissolving the water insoluble compound and the lipid conjugated polymer in an organic solvent, removing the organic solvent and hydrating the lipid film to form micelles. The Patent Office has noted that the reference does not provide the conditions of temperature and pressure under which the organic solvent is removed before hydration nor are the recited ratios of to mPEG-DSPE to AmB taught. In addition, dextrose is said to be taught by Onyuksel as a cryopreservative. The Patent Office has concluded that it would have been obvious to manipulate the basic teachings of the cited patent to obtain micelles with the desired amounts of the active agents.

Applicant has reviewed the cited Onyuksel reference and note that, in general and in the specifically exemplified methods disclosed therein, the PEG-DSPE is dissolved in an organic solvent (i.e., chloroform), dried to prepare micelles and then **after hydration**, the hydrated micelle-containing material is mixed with the biologically active agent. It is specified in Onyuksel's claim 1 that the biologically active material becomes associated with the sterically stabilized micelles. There is little disclosure related to making micelles with a different strategy, and that limited disclosure for mixing polymer and active agent does not provide for the combination of Am B with polymer.

Onyuksel does not disclose that a polyene antibiotic-containing antibiotic preparation (made by the method of Onyuksel) would contain **deaggregated** antibiotic (for example, Am B). The present invention relies on **deaggregated** Am B as a means for minimizing hemolytic (toxic) activity while providing a soluble formulation of this difficult-to-administer therapeutic agent. The presently claimed preparation method allows for the association of the polyene antibiotic with PEG-DSPE in a way which prevents aggregation of antibiotic when hydrated, i.e., which produces micellar deaggregated antibiotic, thus minimizing its toxicity (as measured by hemolysis). Thus the cited Onyuksel actually teaches away from the present claimed method for providing a polyene antibiotic formulation which is soluble and has reduced toxicity (due to deaggregated state) as compared to known prior art compositions, either with respect to the polymer carrier or aggregated polyene antibiotic. Onyuksel does not appear to make any distinction between aggregated and disaggregated material and the advantages of the deaggregated AmB over the aggregated material (which is known to be toxic) in therapy.

Onyuksel teaches a molar ratio of polymer to bioactive molecule of 125:1 and 250:1 in Examples 4, 5, and 7, for example, and a ratio of polymer to bioactive

molecule of about 50:1 in Example11, which does not involve any solvent and does not involve any evaporation step. Certain examples do not unambiguously present ratios. Example 12 teaches detergents in the mix – bile salts, which (detergents) can also contribute to toxicity of AmB-containing materials.

There is nothing in the cited reference which would lead to a reasonable likelihood of success in the current claimed invention, in that a different strategy is employed and there was no teaching of a need for a different strategy for formulations or a need for a deaggregated form of drug, as is important in the case of the polyene antibiotics, especially Amphotericin B. There is nothing on the record which would lead one of ordinary skill in the art to believe that the instant claimed process and that of Onyuksel were interchangeable.

Furthermore, the present Specification teaches the production of micelles in which the polyene antibiotic is deaggregated. This does not appear to be taught by the cited Onyuksel reference, and Applicant respectfully maintains that this is an advantage of the present invention (aggregated Am B, for example, is toxic). Claim 1 has also been amended to specify that the polyene antibiotic is **deaggregated**. The importance of deaggregation and toxicity are discussed in the application at page 12, first paragraph, for example.

Finally, Applicant notes that the cited portion of Onyuksel relates to the preparation of a **crystalline** product or a sterically stabilized micelle preparation (col. 14, lines 15-47, claims 7-11 and 31). Onyuksel acknowledges that the "crystalline product of the method is essentially a micelle-encased **aggregate** of the **insoluble** compound which is densely packed and crystallized" (column 14, lines 12-15; emphasis added). The present invention, as set forth in claims 1-14, by contrast, does not relate to a crystalline polyene product, but rather relates to micelles which contain a deaggregated product, including new claim 15 which specifies the deaggregated state

of the Am B. In addition, claims 12-15 specify the ratio of amphiphilic polymer and Am B.

Moreover, claim 1 contains a limitation as to the temperature for hydration of the dried layer (in step (b), adding water at a temperature from 25°C to 80°C to the drug-polymer film) which does not appear to be taught or suggested in the cited reference. Thus, it appears that the cited reference does not teach or suggest this aspect of the present claimed invention.

Applicants respectfully note that claim 8 specifies a particular polymer (mPEG-DSPE) and a particular polyene antibiotic (AmB) and that the antibiotic and the poly(ethylene glycol)-phospholipid are present at a molar ratio of from 0.75:1 to 10:1. The ratios of antibiotic to polymer taught in the cited Onyuksel patent are believed to be greater than as in the currently claimed methods. It is a surprising result in the present application that stable micelles containing deaggregated polyene antibiotic can be made with such a low ratio of polymer to drug, and there was nothing in the cited reference that would have led one of ordinary skill in the art to believe that there would have been a reasonable probability of success in using such a ratio as claimed.

Claims 1-15 are not rendered obvious by the cited reference because Onyuksel fails to teach, enable or suggest all the limitations of the instant claims, in particular for a method of making micelles comprising a deaggregated polyene antibiotic and with the polymer and antibiotic at the specified ratio.

In view of the foregoing, Applicant respectfully submits that there has been no *prima facie* case for obviousness made out, and the withdrawal of the rejection is requested.

Claims 1-14 were rejected under 35 U.S.C. 103 as allegedly unpatentable over Allen (2004/0013717) by itself or Allen in view of Yu et al. (1998). Applicant respectfully traverses this rejection.

Allen is said to teach micellar formulations containing PEG-DSPE to deliver any chemical or biologically active agent. The method of preparing was said to involve dissolving the active agent and the phospholipid in an organic solvent, evaporation using a rotary evaporator increasing the vacuum in 25 mbar increments and hydrating the lipid film to form the micelles. The compositions could be freeze-dried in the presence of a cryoprotectant such as a saccharide and rehydrated before use. The weight of PEG is between 1000 and 10,000. The Patent Office concluded that it would have been obvious to use any active agent, including Am B, with a reasonable likelihood of success since Allen taught allegedly general applicability.

Applicant does not see that the cited Allen reference, which only aspirationally suggests any chemically or biologically active molecule, and more specifically teaches incorporation of photosensitizing agent into the micelles, to be incorporated into micelles, actually suggests the use of a polyene antibiotic or why one of ordinary skill in the art would choose this particular strategy from the myriad of strategies for formulating such antibiotics known to the art. Many references relating to strategies for providing polyene antibiotics, including Am B, are known to the art.

It is noted that the cited Allen reference focuses on the solubilization of photosensitizing compounds using amphiphilic polymers. The photosensitizers are related to porphyrins, which are characterized as relatively rigid planar molecules. By contrast, the polyene antibiotics of the present methods are relatively flexible molecules. Because of the differences in the structure and physical conformations of Allen's photosensitizers and the present polyene antibiotics, Applicants respectfully submit that the teachings of the Allen reference would not have suggested the present

claimed invention to one of ordinary skill in the art, nor would the teachings of the cited Allen reference has provided for any reasonable probability of success in the present invention.

Allen focuses on photosensitizers, and only suggests the use of "any chemically or biologically active agent". This represents a vastly broad class of molecules, of which the polyene antibiotics are a small class. Notably, Allen does not specifically teach antibiotics such as the polyenes. Allen does not appear to make any statements or teachings concerning temperatures for the hydration step, as specified in the present claims. Notably, the present claims specify that the antibiotic is deaggregated in the micellar preparations. It is also taught that rehydration temperature is important; see the as-filed Specification in the paragraph bridging pages 10-11. There was nothing in Allen which related to the importance of temperature, nor was there any teaching of the desirability of any particular ratios of polymer and polyene antibiotic.

Accordingly, Applicant respectfully submits that there is no *prima facie* case for obviousness made out with respect to the Allen reference, and the withdrawal of the rejection is respectfully requested. However, in the interest of advancing prosecution and without acquiescing to the rejection, claim 1, subparagraph (a) has been amended to specify that the antibiotic and the poly(ethylene glycol)-phospholipid are present at a molar ratio of from 0.75:1. This is supported by as-filed claim 8.

Yu is said to teach polymeric micelles for delivery of Am B, specifically where the polymer was a PEG derivative of benzyl-aspartic acid, and the use of such micelles to reduce hemolysis by Am B. The Patent Office has alleged that one would have been motivated to use Am B in the micelles of Allen with a reasonable expectation of success since the cited Yu reference showed the knowledge of the art of Am B and polymeric micelles to reduce the hemolytic activity of Am B. Alternatively, the use of PEG-DSPE instead of PEG-block-β-benzyl-aspartate would allegedly have been obvious to one of

ordinary skill in the art since the reference of Allen showed that PEG-DSPE also formed micelles and such micelles could be used for delivery of active agents. The Patent Office concedes that Allen did not specifically teach dextrose as saccharide but has alleged the use of any saccharide would have been obvious to one of ordinary skill in the art with a reasonable expectation of success.

The cited Yu reference has provided an alternative strategy to that claimed for formulating Am B. It teaches a different polymeric material (PEG-poly β-benzyl-L-aspartate), and it teaches a different method (dialysis) for the preparation of micelles. Thus, it leads away from the present claimed invention, as there is no indication that various components such as the amphiphilic polymers are interchangeable or that method steps associated with one material can successfully be used with other materials. In addition, Yu does not provide any teaching or suggestion relating to the temperature range for a hydration step, as in the present claimed invention. Furthermore, the Yu reference does not appear to teach or suggest any deficiency of the compositions taught therein; accordingly, on that basis, there would be no motivation to seek improvement, or to combine the teachings of Yu with the cited Allen reference. Applicant respectfully points out that the various methods available for the preparation of micelles are not interchangeable for all micelle forming materials and for all incorporated molecules such as polyene antibiotics. Certainly there was no teaching of the temperature range in step (c) of claim 1. Thus, it would not have been the requisite probability of success in varying materials and methods from reference to reference, and it would require the use of hindsight to choose the operable combinations of the teachings of the prior art. Applicant respectfully states that the combination of the Allen and the Yu references would not lead to the present claimed invention.

With respect to the composition claims (claims 12-15), there is no teaching of micelles containing Am B in the cited Allen reference, and in Yu, it is taught that

compositions should be formulated with a PEG-block-poly(β-benzyl-aspartate), which is not a PEG-phospholipid, and prepared with a dialysis step. In addition, neither cited reference teaches or suggests the deaggregated state of Am B in the claimed compositions of claims 12-15, nor is there teaching of the advantage of any particular temperature range for hydrating a dried film of material.

It is Applicant's position that these references, alone or in combination, did not provide the requisite teachings or probability of success to support a conclusion of obviousness. In combination they might be asserted to yield a PEG- block-poly(β-benzyl-aspartate) preparation containing a photoactive agent. Such a combination does not plausibly have relevance to a polyene antibiotic in combination with a PEG-phospholipid, as set forth in the present claims, and there would have still been lacking the recited temperature range in the method steps.

In sum, Applicant respectfully maintains that the present invention as claimed is not obvious over the cited references, and the rejection should be withdrawn.

Claim 14 was rejected under 35 U.S.C. 103 as allegedly unpatentable over Onyuksel (6,217,886) or Allen (2004/0013717) by itself or in view of Yu et all (1998) or vice versa as set forth above in view of McShane (6,906,042). Applicant respectfully traverses this rejection.

The Patent Office has characterized the cited McShane patent as disclosing micellar formulations rehydrated with a dextrose solution, which is suitable for intravenous administrations.

The disclosure of McShane appears to relate to micelles having a very specific compound of Formula A. The structure of Formula A bears essentially no relationship to any component of the micelles formed in the claimed methods and compositions of

the instant application. Thus, apart from the common use of the term "micelles" and the mention of "dextrose", the disclosure of McShane is not relevant to the patentability of the present claimed invention. McShane does not appear to disclose antibiotics, let alone polyene antibiotics in deaggregated or any other form. McShane makes no teaches of ratios nor of particular advantageous temperatures for micelle formation. Moreover, McShane teaches dissolution of materials using alkaline solutions, in particular a lipopolysaccharide analog. There is no teaching related to the combination of a polyene antibiotic with a polyethylene glycol-phospholipid polymer to form micelles. There is no specific basis for any teaching suggestion or motivation to combine McShane with any of the other cited references. McShane, with its disclosure of a cryoprotectant and lyophilization, does not remedy the shortcomings of the Onyuksel, Allen and Yu references.

The other references have been discussed above, and Applicant has made the case for patentability of the claimed methods for preparing micellar compositions containing polyene antibiotics such as Am B. It is the deaggregated state of the polyene antibiotic, which is a important feature of the present claimed invention, which follows from carrying out the claimed method steps, including the temperature range over which the hydration step is performed, and with respect to Onyuksel, the steps for preparation of the micellar compositions which are distinguished from the present methods. It was a significant achievement to produce solubilized, deaggregated Am B preparations which were not characterized by relatively high levels of solubilizing agent to drug, i.e., PEG-DSPE, as was the case in certain prior art formulations, e.g., Barwicz et al. (1992) *Antimicrobial Agents and Chemotherapy* 36:2310-2315, already of record. It is Applicant's position that the present claimed methods and ratio of polymer to drug lead to the improved properties of those compositions and that the results obtained were unexpected.

Accordingly, no *prima facie* case for obviousness of the present invention has

been made out, and the withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Request for Continued Examination, a Petition for Extension of Time and payment of the necessary fees. It is believed that this response does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If this is incorrect, however, please deduct as necessary from Deposit Account No. 07-1969.

Respectfully submitted,

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